

Efficient Catalysis in Dynamic Nanomicelles of PS-750-M Suspended in Water

Gaganpreet Kaur,[#] Karanjeet Kaur,[#] Sachin Handa*

Department of Chemistry, University of Louisville, 2320 S. Brook Street, Louisville, Kentucky 40292, United States
Email: sachin.handa@louisville.edu

[#]These authors equally contributed

Abstract: This review demonstrates the multiple roles of surfactants in aqueous micellar catalysis. It covers the design and recent applications of proline-based amphiphile PS-750-M, including completely organic solvent-free amide couplings, C–H fluorination of arenes and heteroarenes achieved via radical pathway facilitated by the shielding effect of micelles. In addition, it critically sheds light on selective hydrogenolysis and cross-couplings of water-sensitive acid chlorides in water catalyzed by phosphine ligand-free Pd(0) nanoparticles. The metal-micelle interaction responsible for catalytic activities probed by various spectroscopic techniques is also discussed.

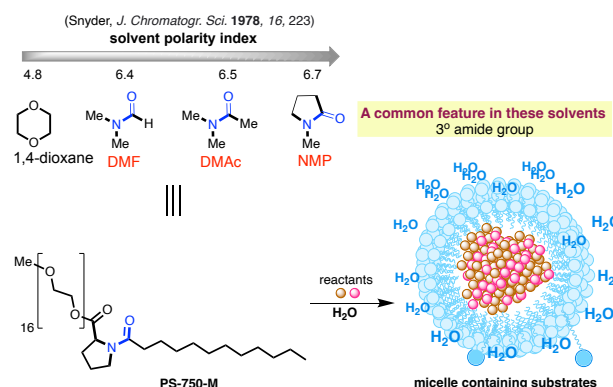
Keywords: Amphiphile, Micelle, Nanoparticles, Amide couplings, Cross-couplings

Introduction. Water is the most abundant solvent in Nature [1,2]. However, its **usage** as a solvent is limited due to the insolubility of catalyst, reactants, and the product [3]. Besides, the sensitivity of reaction intermediates in water further limits its use, despite its greenness and benign nature. It has potential to offer better chemistry if used in ways that are closely aligned with the natural phenomena [4-6]. For example, in natural biocatalysis, the substrate binds with the hydrophobic catalytic pockets of enzyme molecules for bond breaking and bond-making events to release the final product to the medium, i.e., water [7]. In this process, enzymes are water-soluble, and it does not matter whether the reactants are highly soluble in water or not—the catalytic events happen within the enzymatic pockets; water is only a medium. Likewise, such hydrophobic pockets can be attained by dissolving amphiphile molecules in water. Amphiphile molecule generally contains hydrophilic (water-soluble) and hydrophobic (water-insoluble) parts. Due to the optimal balance between hydrophilicity and hydrophobicity, amphiphile molecules self-aggregate when dissolved in water at above critical micelle concentration. The thermodynamically driven self-aggregation or micelle-forming process is dynamic, allowing the exchange of the catalyst, reactant, and product between micelles and micelle and water. The extent of hydrophobicity and chemical functionality of amphiphiles in micellar interior assist in determining the reaction rate, selectivity, and broader activity. Therefore, the nature of micelles interior plays a crucial role in micellar catalysis [8].

The micellar catalysis originated in the early 20th century with the Twitchell process [9]. This area of research gained attention from organic chemists with the report on dehydration reactions in aqueous micelles achieved by Kobayashi and coworkers [10]. In 2009, Lipshutz and coworkers' report on Negishi couplings in aqueous surfactant without preformation of the organozinc reagents showcased the power of micellar catalysis [11]. Reports from Lipshutz [12-14], Kobayashi [15], and Uozumi [16] on robust, general, and industrially viable protocols in micellar media further helped advance the field of sustainable chemistry. Instead of just micellar catalysis, our group has significantly advanced the *micellar nanocatalysis* by aiming to mimic toxic dipolar-aprotic solvents with a single amphiphile while offering robust water-compatible nanocatalysts.

Our journey started with designing a proline-based amphiphile, PS-750-M (also called FI-750-M) [17]. We aimed to replace toxic dipolar-aprotic solvents (DMF, NMP, 1,4-dioxane), while simultaneously understanding how and why micellar catalysis works better than traditional chemistry [18,19]. We also covered applications of PS-750-M for new reactions while offering a solution to existing problems in known transformations. Reports on the replacements of dipolar-aprotic solvents have also appeared in the literature. Switchable solvent piperylene sulfone had been successfully employed to replace DMSO for many-valued transformations [20]. The negative side of this approach includes the release of toxic SO₂ at elevated temperatures. Cyrene is another recently popular replacement for NMP [21]. It has an active methylene group that could actively react with reactants. Replacing a toxic organic solvent with a green but self-reactive solvent may pose limitations. Therefore, the aqueous micellar catalysis approach may be better than replacing one organic solvent with another.

Figure 1



Designer surfactant PS-750-M. Amphiphile structurally mimics dipolar-aprotic solvents.

A micelle's broad size distribution, dynamic nature, and exchange process help to mimic various dipolar aprotic solvents with aqueous micelles of a single amphiphile. In matching the solvent polarity of extremely useful but toxic dipolar-aprotic solvents, we devised the amphiphile PS-750-M (Figure 1). We designed amphiphile PS-750-M based on these

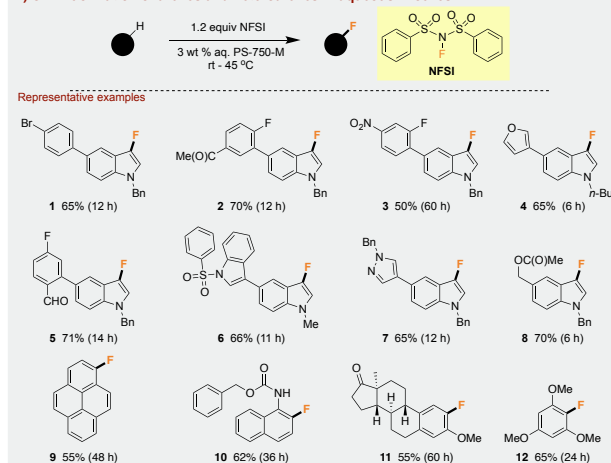
guiding principles: (i) resulting micelles should be self-non-reactive; (ii) the optimal polarity of micellar core achieved by an introduction of tertiary amide groups should enhance the solubility of polar reactants and stability of NP catalyst. PS-750-M has a tertiary amide functional group connecting a polar mPEG chain with the non-polar hydrocarbon chain via a proline linker. With an optimal balance between hydrophilic and lipophilic chains, the PS-750-M, upon dissolution in water (CMC *ca.* 10^{-6} M), instantly forms micelles containing the tertiary amide group in the micellar core or interface, which assists in matching its activity with dipolar-aprotic solvents. Under mild conditions, the micelles of PS-750-M were proven effective for selective sulfonylation of perfluoroarenes [18], highly selective monofluorination of indoles and arenes [22], selective Cbz cleavage [23], amide couplings [24,25], and a variety of metal nanoparticle-catalyzed cross-coupling reactions. Besides, we have investigated the reactivity of carbene [24], carbanion, and keteniminate intermediates [27] under the shielding effect of micelles. Moving forward, we have also achieved selective carboxylation of aryl halides via the possible involvement of trichlorocarbanion species (unpublished). In this article, we only discuss some of key metal-free transformations and cross-couplings enabled by phosphine ligand-free nanoparticle catalyst in aqueous PS-750-M

Metal-Free Chemistry Mediated by Nanomicelles of PS-750-M. The advent of chemistry in water using benign surfactants has tremendously gained visibility, triggering applications to reactions that are otherwise not cleanly possible in any organic solvents [28]. The reaction profile in the micellar medium is generally better than the organic solvents. This is due to the underlying hydrophobic effect responsible for the higher concentration of reactants and the catalyst in the micellar interior, resulting in fast reaction rates and higher yields with improved selectivities [8]. The high selectivities are reported for monofluorination reactions of indoles and arenes, where the shielding effect of micelles facilitates the radical pathway, enabling site-selective electrophilic fluorination [22]. Likewise, better selectivity and fast reaction rates are reported for epimerization- and organic solvent-free amide couplings [24,25]. These projects were completed in collaboration with Novartis and AbbVie, respectively. These transformations are facile and scalable.

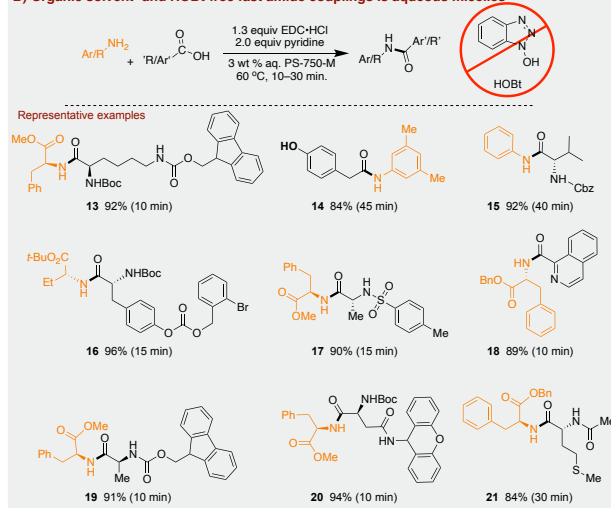
(a) Monofluorination of indoles and arenes. Methods for introducing the fluorine group at the C-3 position of indole were not known before our report. It may be due to the spontaneous and simultaneous oxidation process, leading to fluorinated oxindole formation [29]. Previous methodologies to prevent further oxidation have been developed, such as protecting the C-2 position of indole [30] or fluorination of the C-3 position of indole precursors before indolization [31,32]. However, such methodologies involve non-sustainable protection-deprotection steps, decreasing the step economy while not eliminating the side products. In 2019, our group reported one-step oxidation-free fluorination of indoles and arenes [22]. In this report, we harnessed the shielding effect of micelles of PS-750-M to facilitate the radical pathway that is more selective. Readily available fluorine source *N*-fluorodi(benzenesulfonyl)amine (NFSI) worked well for this selective transformation. A low concentration of oxygen inside the core of the micelle prevents further oxidation of the fluorinated product, yielding oxindole-free fluorinated products. Remarkably, base and an excess fluorinating agent were not required. In this system, PS-750-M mimics dipolar aprotic sol

Figure 2

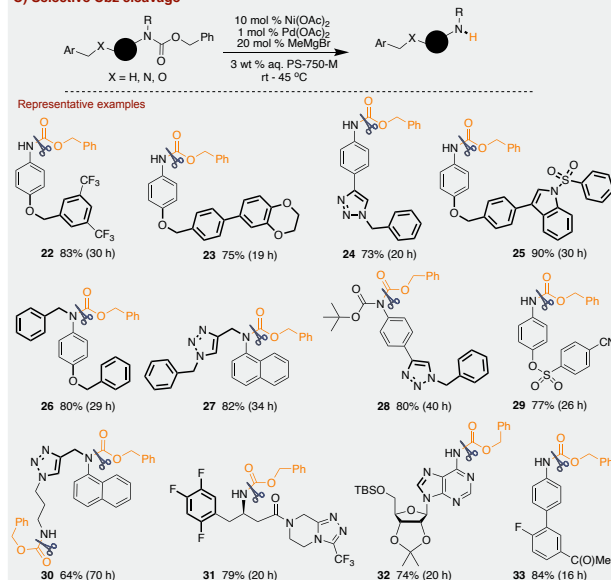
A) C–H fluorination of arenes and heteroarenes in aqueous micelles



B) Organic solvent- and HOBt-free fast amide couplings in aqueous micelles



C) Selective Cbz cleavage



Applications of PS-750-M in metal-free transformations and selective hydrogenolysis. (A) C–H fluorination of arenes and heteroarenes. (B) Epimerization- and completely organic solvent-free fast amide couplings. (C) Highly selective hydrogenolysis for Cbz cleavage in the presence of other sensitive groups (Adapted with permission from *ACS Catal.* 9 (2019) 7520; *Org. Lett.* 22 (2020) 5737; *ChemSusChem* 12 (2019) 3037. Copyright (2022) American Chemical Society and Wiley-VCH).

-vent. Most likely fluorination agent remains at the interface. During the exchange of amphiphiles between the micelles, the radicophile traps the fluorine radical to generate desired product.

Notably, the desired transformation was impossible in neat water or organic solvents. When attempted, only the formation of *N*-benzylisatin and other oxidized products were formed. The order of addition was crucial for the reaction's success. The sequential addition of indole in 3 wt % aqueous PS-750-M and NFSI affords better yields. The slower addition of NFSI and THF co-solvent significantly improved the reaction yields. After reaction completion, a minimal amount of EtOAc (generally 50% volume of the aqueous layer) was added to the reaction mixture while stirring at rt for a minute. This pulls the product into the organic layer from the aqueous microemulsion. Only organic product or byproduct goes into the EtOAc layer, while PS-750-M remains in the aqueous layer to be re-used. The representative examples are shown in Figure 2A, demonstrating the functional group tolerance and the generality of the protocol. Halogens, ester, nitro, ether, aldehyde, and ketone functionalities were well tolerated (1-12). No aldol-type reactions and aldehyde oxidation were observed in examples 2 and 5, respectively. The fluorination was primarily selective to indole's 3-position—no fluorination happened at the pyrazole ring in the example of pyrazole-containing indole 7. Likewise, furan (4) and sulfonyl indole (6) rings remained intact. The presence of electron-withdrawing groups, such as nitro leads to prolonged reaction times owing to the -I effect. This protocol was only applicable to *N*-protected indoles. The reaction did not work for the indoles containing free NH group.

In the same report, the authors also explored the reaction mechanism. Control experiments using BHT and TEMPO in the reaction mixture and GC-MS analysis of the reaction mixture supported the radical pathway for fluorination. The 6.2 E factor and recyclability of the reaction medium for up to four cycles further support the sustainability. Most notably, the same transformation in TPGS-750-M or Nok or Tween 20 was ineffective. Low desired product yield and significant amounts of undesired fluorinated-and non-fluorinated oxindole byproducts formation were observed.

(b) Completely organic solvents-free fast amide couplings in water. The amide coupling reaction is one of the most valuable reactions for the pharmaceutical industry [33,34]. Before our group started investigating this reaction, there were not any known methods for the amide couplings that are epimerization- and organic solvents- free. The Lipshutz methodology involving COMU as the coupling agent and TPGS-750-M as amphiphile requires organic solvents for product extraction and purification [33]. However, the reported yields were quite impressive. In aiming for fast reaction rates to avoid epimerization of product, eliminating column chromatography, and product extraction with the organic solvent, we harnessed the structural feature of 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) [24,25]. It is commercially available in the EDC•HCl form. Its amphiphile-like structure facilitates the formation of mixed micelles when dissolved in 3 wt % aqueous PS-750-M. The formation of mixed micelles ensures the presence of reactants and coupling agents within the micelle. Their higher concentration causes fast reaction rates without the product's epimerization. The presence of new amide bond resulting in less solubility of the product in the micelle helps releasing the product into water.

Upon simple filtration, we extracted desired product. Notably, the nature of the base was crucial for the success of this technology. The strong bases, such as Et₃N and *i*-PrNEt₂, did not serve the purpose. Based on NMR studies, these bases freed-up the HCl salt of EDC to lose its amphiphile-like structure. Therefore, EDC no longer participates in the formation of mixed micelles. This HOBt-free technology was proven safe, selective, scalable, and efficient. The only concerning point of this protocol was the use of pyridine. We are currently developing a new technology that will exclude a pyridine base and water-soluble urea-type waste.

The detailed epimerization studies revealed that the protocol is epimerization-free. Besides, the selectivity was excellent. The representative examples 13-21 are shown in Figure 2B. Under aqueous basic conditions, the Fmoc protecting group and carbonate ester functionality remained intact (13, 16, 19). Surprisingly, the free-OH group remained intact and did not participate in byproduct-forming side reaction (14). No hydrolysis of the methyl ester functional group was observed (17, 19, 20). The methodology was also tested on multigram scale reactions where 14 and 15 were synthesized in excellent isolated yields. Calculated PMI (Process Mass Intensity) for their synthesis were 17.56 and 19.83, respectively, which further strengthened the greenness and sustainability of this approach [25].

Sustainable and Selective Organometallic Catalysis.

Besides metal-free catalysis, we have vastly explored the aqueous micelles of PS-750-M in catalytic reactions involving organometallic nanoparticle catalysts. The remarkable selectivity in deprotection of the Cbz group in the presence of halogens, nitrile, and a variety of benzyl groups was reported by our group. Likewise, recently, we have reported the formation of Pd(II) and Pd(0) nanoparticles stabilized by carbonyls of PS-750-M to facilitate cross-coupling chemistry while eliminating the reliance on phosphine ligands.

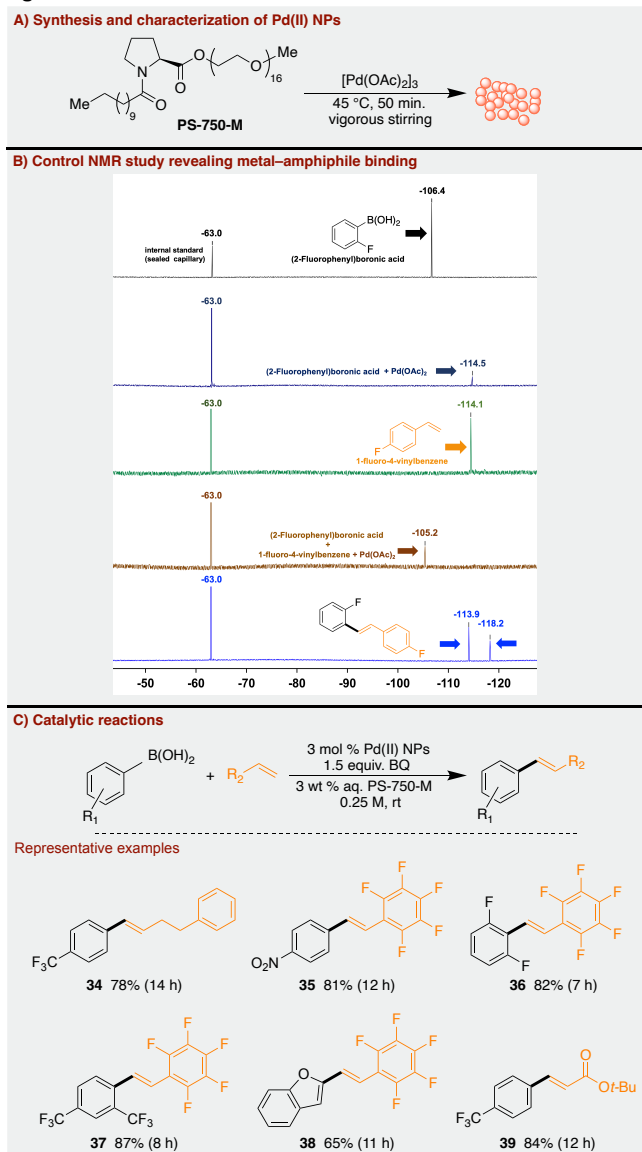
(a) Selective deprotection of Cbz group. The protection of amines with the Cbz group is one of the most critical reactions in multistep organic syntheses. Its deprotection in the presence of other protecting/functional groups, for instance, *O*-benzyl, *N*-benzyl, aldehyde, ketone, and nitrile, is limited due to the sensitivity of these groups to hydrogenolysis.

Recently, our group has addressed this issue using ligated Ni/Pd bimetallic nanoparticles. These nanoparticles contain both Ni and Pd in their zero oxidation states [23]. Notably, these oxidation states are crucial for the desired selectivity to cleave the Cbz group in the presence of other sensitive groups. Ni(OAc)₂/Pd(OAc)₂ (in 10:1 ratio) and 3,4,7,8-(Me)₄-1,10-phenanthroline, when dissolved in THF and subsequently treated with 2.0 equivalents MeMgBr followed by capping the resulting nanoparticles with aq. PS-750-M, forms bimetallic Ni(0)/Pd(0) nanoparticles. These nanoparticles are active for selective Cbz cleavage under ambient hydrogen gas atmosphere or in the presence of NaBH₄ reductant. The micellar environment shields the catalyst from air and water, assist maintaining desired oxidation states of Pd and Ni.

Besides, the catalyst efficiency can be attributed to a higher concentration of hydrogen inside the micelle. A broad substrate scope reveals that the protocol is general and can be applied to complex substrates. Good-to-excellent yields were documented with diverse scope (see representative examples 22-33, Figure 2C). Control experiments suggested

that a 1-month aged catalyst worked as effectively as the fresh catalyst. **The catalyst was also recyclable.**

Figure 3



Palladium (II) nanoparticle catalysis. (A) Synthesis of nanoparticles in aqueous PS-750-M. (B) Control ^{19}F NMR study probing the catalytic activity of nanoparticles. (C) Oxidative Mizoroki–Heck couplings. (Adapted with permission from *JACS* Au. 1 (2021) 308. Copyright {2022} American Chemical Society).

b) Ligand-free oxidative Mizoroki–Heck-type couplings. We developed phosphine ligand-free ultrasmall Pd(II) nanoparticles for oxidative Mizoroki–Heck-type couplings under an aqueous micellar environment [36]. The synthesis of nanoparticles was facile, and did not require inert atmosphere and any organic solvents (Figure 3A). The amphiphile PS-750-M played a vital role in these nanoparticles' stabilization and the catalytic activity. The hypothesis for the formation of nanoparticles in aqueous PS-750-M includes the binding of amphiphile with Pd through its carbonyl functional groups, enhancing its solubility and stability in the micelles. In other words, this metal-micelle binding prevents clumping of Pd nanoparticles and polymerization of nanoparticles precursor. The nanoparticles were characterized by various spectroscopic techniques, such as high-resolution

transmission electron microscopy (HRTEM), energy dispersive X-ray analysis (EDAX), and X-ray photoelectron spectroscopy (XPS). The studies revealed that the particles remained in the form of 50-60 nm aggregates. Upon stirring, these large aggregates release ultrasmall nanoparticles in the form of an active catalyst.

The metal-amphiphile interaction was thoroughly studied by IR and mass spectroscopy. A characteristic shift in the carbonyl signals of ester and amide functional groups of PS-750-M and Pd(II)-bound PS-750-M revealed the Pd-amphiphile binding. Likewise, HRMS analysis of nanoparticles containing an aqueous solution of PS-750-M supported the association of Pd with the amphiphile.

The catalytic reactivity of nanoparticles was established by control NMR studies for the oxidative Mizoroki–Heck-type coupling of arylboronic acids and terminal olefins (Figure 2B). In control study, (2-fluorophenyl)boronic acid and 1-fluoro-4-vinylbenzene were dissolved in aqueous PS-750-M and subsequently analyzed for ^{19}F NMR. In the analysis, their ^{19}F signals appeared at -106.4 and -114.1 ppm, respectively. In contrast, (2-fluorophenyl)boronic acid in nanoparticles in aqueous PS-750-M displayed a signal at 114.5 ppm, revealing the binding of nanoparticle and boronic acid. Likewise, 1-fluoro-4-vinylbenzene mixed with nanoparticles showed a chemical shift at -105.2 ppm, confirming the interaction of olefins with the Pd. Combining arylboronic acid and -fluoro-4-vinylbenzene with Pd nanoparticles forms a coupling product, supported by the appearance of two ^{19}F signals at -113.9 and -118.2 ppm originated from the coupling product (*E*)-1-fluoro-2-(4-fluorostyryl)benzene. The addition of oxidant and another equivalent of coupling partners to the mixture further supported that the nanoparticles are catalytically active.

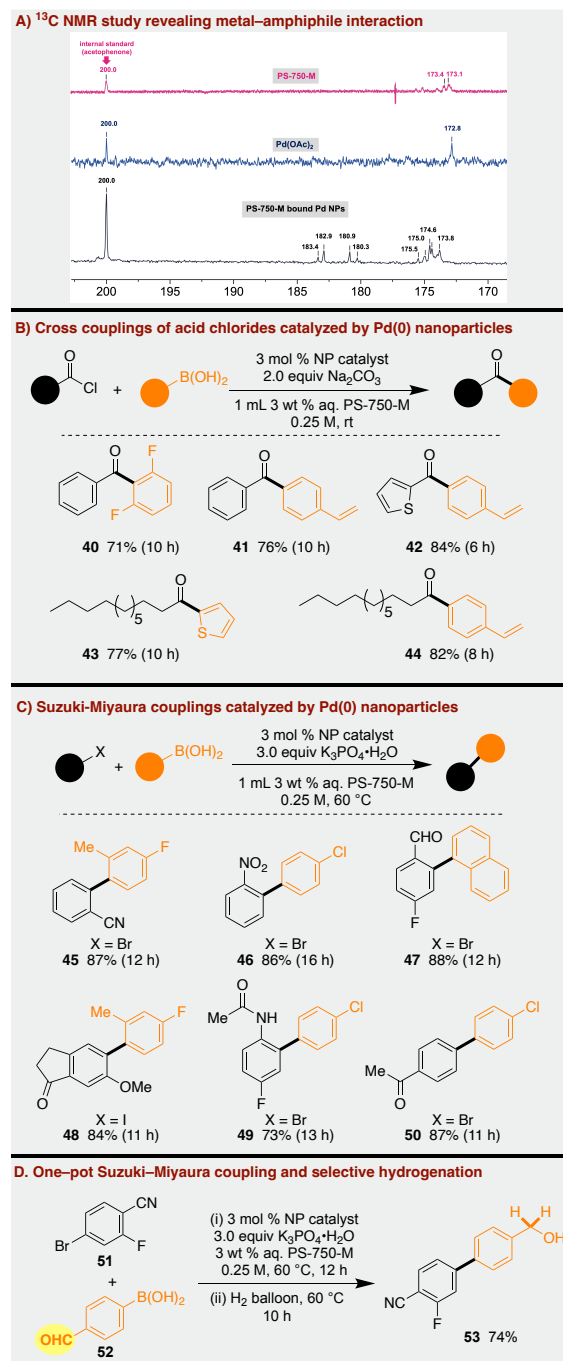
The stirring rate was critical for the reaction outcome. The stirring rate between 1,000-1,500 rpm was optimal. The catalytic activity was explored on 28 different substrates; the representative examples are shown in Figure 3C (**34–39**). The nitro functional group was well tolerated (**35**). Both electron-deficient coupling partners reacted well and provided good-to-excellent yields (**35–37**), featuring this transformation's difference from the classical Heck reaction. Notably, in traditional Heck couplings, reaction proceeds efficiently with electron-rich electrophile and electron-deficient styrene or vice-versa. The non-aromatic olefin coupling partner displayed an excellent desired reactivity (**39**). The scalability of this method was demonstrated on a 100-gram scale reaction. Only 1 mol % catalyst was used that further supports the greenness and sustainability of this protocol. **The catalyst was not fully recyclable.**

(c) Ligand-free cross-coupling of water-sensitive acid chlorides in water. We further explored the phenomena of the micellar shielding effect and metal-micelle binding on Pd(0) nanoparticles [37]. To obtain Pd(0) nanoparticles, we simply treated our Pd(II) nanoparticles with phenylboronic acid and base. The double transmetalation by phenyl groups of the boronic acid, followed by reductive elimination after gentle heating, generates Pd(0) nanoparticles.

The resulting nanoparticles were thoroughly characterized by various spectroscopic techniques to study morphology, size, distribution, elemental analysis, and Pd oxidation state. The Pd(0)–amphiphile interaction was probed by ^{13}C NMR spectroscopy (Figure 4A). The carbonyl signals of the ester

and amide groups of PS-750-M appeared at 173.4 and 173.1 ppm, while $\text{Pd}(\text{OAc})_2$ appeared at 172.8 ppm. However, the $\text{Pd}(0)$ nanoparticles in aqueous PS-750-M displayed multiple signals at 175.5–173.8 ppm revealed the formation of different sized micelles. The downfield signals at 183.4–180.3 ppm supports the metal–amphiphile interaction.

Figure 4



Phosphine ligand-free $\text{Pd}(0)$ nanoparticles in aqueous PS-750-M. (A) Control NMR studies for probing metal-micelle binding. (B) Cross-couplings of acid chlorides in aqueous PS-750-M catalyzed by $\text{Pd}(0)$ nanoparticles. (C) Activity of nanoparticles for Suzuki-Miyaura couplings. (D) One-pot Suzuki-Miyaura couplings and carbonyl reduction catalyzed by $\text{Pd}(0)$ nanoparticles in micellar medium. (Adapted with permission from JACS Au 1, (2021) 1506. Copyright {2022} American Chemical Society).

These nanoparticles were tested for their catalytic activity for cross-couplings of water-sensitive acid chlorides. The sequential addition of catalyst, boronic acid, base, and acid chloride was critical. The reaction works well as long as acid chloride is added in the end to ensure that all the reaction components are compartmentalized before the acid chloride is available for the desired reaction. The micelle's shielding effect plays a crucial role in preventing hydrolysis of acid chlorides under basic pH—neat water was detrimental. The substrate scope was explored on combinations of acid chlorides and aryl and (hetero)arylboronic acids. Representative examples are shown in Figure 4B (45–50). In these examples, a unique selectivity was observed, and no side-reaction was observed at the terminal olefin center (41, 42, 44). Both (hetero)aryl and alkyl acid chlorides displayed excellent reactivity. Notably, no byproduct from β -H elimination was observed in example 44. The fate of acid chloride was tested under reaction conditions using benzoyl chloride, indicating a half-life of 1 h, supporting that a boronic acid coupling partner is responsible for the enhanced stability of acid chloride under aqueous micellar environment.

The catalytic activity of these nanoparticles was also tested on ligand-free Suzuki-Miyaura couplings (Figure 4C). As depicted in the representative examples, excellent functional group tolerance was observed. The nitrile (45), nitro (46), formyl (47), and ketone (48) amide (49) were well tolerated. The substrates susceptible to α -arylation (48) showed no byproduct formation. No undesired cross-coupling at the chloro center or dechlorination was observed when bromochloroarene was used as the coupling partner; only the desired product was obtained in excellent yield with the retention of chloro functional group (50). The application of this technology was also showcased on one-pot reaction, i.e., Suzuki coupling and hydrogenation of aldehyde (Figure 4D). In this transformation, coupling partners 51 and 52 cleanly afford cross-coupling products, which provides product 53 in 74% isolated yield upon hydrogenation. **Notably, these NPs were non-recyclable.** Hopefully, with a demonstration on a broader scope, this technology will sooner be implemented to one pot- Suzuki couplings and asymmetric hydrogenations.

Conclusions and perspective. The discussion above shows that the micellar catalysis or chemistry in water has more to offer than the content presented in this article or documented in the literature. From our group's contribution, our team has shown that the PS-750-M is an acceptable alternative to toxic dipolar-aprotic solvents and phosphine ligands for cross-couplings of acid chlorides and traditional Suzuki-Miyaura couplings. More challenging reactions can be achieved either with the same amphiphile or may require fine-tuning of the structure of PS-750-M. In unpublished work, we have shown that micellar catalysis and photocatalysis can be combined for efficient, green, and sustainable ppm level $\text{Cu}(\text{I})$ catalysis. Another exciting feature of micellar catalysis is one-pot multistep reactions due to the ability of micelles to mimic a variety of solvents. However, the downside of this aqueous micellar technology includes requirement of EtOAc (an organic solvent) for product extraction and cleaning of water after usage. Notably, only a minimal amount of EtOAc is needed for the workup procedure. Likewise, the aqueous waste generation is significantly less, comparatively produced in traditional catalysis in organic solvents. Noteless, it's still a waste generation, and we are aggressively working to address this issue. Our effort can be recognized by our report on completely organic solvents free amide couplings. Our

significant efforts are now devoted to water cleaning and further mitigate or eliminate usage of organic solvents in micellar technology.

Credit Author Statement

Gaganpreet Kaur – Writing
Karanjeet Kaur – Writing
Sachin Handa – Supervision, editing, and advising

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

SH thanks the National Science Foundation for financial support (CHE-2044778).

References

Papers of particular interest, published within the period of review have been highlighted as:

* of special interest

** of outstanding interest

1. Kitanosono T, Masuda K, Xu P, Kobayashi S: **Catalytic Organic Reactions in Water toward Sustainable Society**. *Chem. Rev.* 2018, **118**:679. <https://doi.org/10.1021/acs.chemrev.7b00417>
 2. Hailes HC: **Reaction Solvent Selection: The Potential of Water as a Solvent for Organic Transformations**. *Org. Process Res. Dev.* 2007, **11**:114. <https://doi.org/10.1021/op060157x>
 3. Cortes-Clerget M, Yu J, Kincaid JRA, Walde P, Gallou F, Lipshutz BH: **Water as the reaction medium in organic chemistry: from our worst enemy to our best friend**. *Chem. Sci.* 2021, **12**:4237–4266. <https://doi.org/10.1039/D0SC06000C>
 4. Lipshutz BH, Ghorai S, Cortes-Clerget M: **The Hydrophobic Effect Applied to Organic Synthesis: Recent Synthetic Chemistry “in Water”**. *Chem. Eur. J.* 2018, **24**:6672–6695. <https://doi.org/10.1002/chem.201705499>
- In this review article, the authors demonstrated the role of micellar catalysis in organic synthesis, which have been able to solve the major problems in C-C, C-H, and C-heteroatom bond formations. Micellar catalysis significantly reduced the generation of organic waste from solvents.
5. Braun MG, Diorazio L, Fraunhoffer K, Hayler J, Hickey M, Latham J, Lovelle LE, McLaws M, Parsons AT, Richardson P, Roiban GD, Roosen PC, Steven A, Terrett JA, White T, Yin J: **Green Chemistry Articles of Interest to the Pharmaceutical Industry**. *Org. Process Res. Dev.* 2020, **24**:334. <https://doi.org/10.1021/acs.oprd.0c00154>
 6. Gallou F, Isley NA, Ganic A, Onken U, Parmentier M: **Surfactant Technology Applied toward an Active Pharmaceutical Ingredient: More than a Simple Green Chemistry Advance**. *Green Chem.* 2016, **18**:14–19. <https://doi.org/10.1039/C5GC02371H>

7. Cortes-Clerget M, Akporji N, Zhou J, Gao F, Guo P, Parmentier M, Gallou F, Berthon JY, Lipshutz BH: **Bridging the gap between transition metal- and bio-catalysis via aqueous micellar catalysis**. *Nat. Commun.* 2019, **10**:2169. <https://doi.org/10.1038/s41467-019-09751-4>
8. Ansari TN, Gallou F, Handa S: **Cross-couplings in Water – A Better Way to Assemble New Bonds**. *Organomet. Chem. Ind.* 2020, **Ch8**: 203–238. <https://doi.org/10.1002/9783527819201>
9. Twitchell E: **A reagent in the chemistry of fats**. *J. Am. Chem. Soc.* 1907, **29**:566–571. <https://doi.org/10.1021/ja01958a019>
10. Manabe K, Imura S, Sun XM, Kobayashi S: **Dehydration Reactions in Water. Brønsted Acid–Surfactant-Combined Catalyst for Ester, Ether, Thioether, and Dithioacetal Formation in Water**. *J. Am. Chem. Soc.* 2002, **124**:11971–11978. <https://doi.org/10.1021/ja026241j>

In this work, surfactant-type catalyst DBSA was used to conduct reactions, such as dehydrative esterification, (thio)etherification, and thioacetalization. The reactions do not need dehydrating agents or azeotropic removal of water. Instead, the catalyst and substrates in the present system assemble together through hydrophobic interactions. This work paved the way to various advances in micellar catalysis.

11. Krasovskiy A, Duplais C, Lipshutz BH: **Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature Without Prior Formation of Organozinc Reagents**. *J. Am. Chem. Soc.* 2009, **131**: 15592–15593. <https://doi.org/10.1021/ja906803t>
12. Lipshutz BH, Ghorai S, Cortes-Clerget M: **The Hydrophobic Effect Applied to Organic Synthesis: Recent Synthetic Chemistry “in Water”**. *Chem. Eur. J.* 2018, **24**:6672–6695. <https://doi.org/10.1002/chem.201705499>
13. Handa S, Wang Y, Gallou F, Lipshutz BH: **Sustainable Fe–ppm Pd nanoparticle catalysis of Suzuki–Miyaura cross-couplings in water**. *Science* 2015, **349**:1087–1091. <https://doi.org/10.1126/science.aac6936>

In this article, the authors developed a sustainable method for Suzuki–Miyaura cross-couplings for highly challenging reaction partners in water. Nanoparticle (NPs) synthesis involves inexpensive FeCl₃ and parts-per-million (ppm) level of Pd, which significantly reduce the reliance on expensive metal Pd. Importantly, NPs are recyclable.

14. Pang H, Hu Y, Yu J, Gallou F, Lipshutz BH: **Water-Sculpting of a Heterogeneous Nanoparticle Precatalyst for Mizoroki–Heck Couplings under Aqueous Micellar Catalysis Conditions**. *J. Am. Chem. Soc.* 2021, **143**:3373–3382. <https://doi.org/10.1021/jacs.0c11484>

15. Kobayashi S: **Sc(OTf)₃-Catalyzed three-component reactions of aldehydes, amines and allyltributylstannane in micellar systems. Facile synthesis of homoallylic amines in water.** *Chem. Commun.* 1998, 19–20. <https://doi.org/10.1039/A706498E>.
16. Uozumi Y, Niimi R: **α -Arylation of Nitriles Catalyzed by Palladium Nanoparticles in Proline-Based Micelles.** *Synfacts* 2020, 16:1085. <https://doi.org/10.1055/s-0040-1706757>.
17. Brals J, Smith JD, Ibrahim F, Gallou F, Handa S: **Micelle-Enabled Palladium Catalysis for Convenient sp^2 - sp^3 Coupling of Nitroalkanes with Aryl Bromides in Water Under Mild Conditions.** *ACS Catal.* 2017, 7:7245–7250. <https://doi.org/10.1021/acscatal.7b02663>.

This article describes the custom designed surfactant FI-750-M, which mimics polar solvents like DMF and 1,4-dioxane, demonstrating palladium-catalyzed sp^2 - sp^3 coupling of nitroalkanes to aryl bromides. FI-750-M decreased the dependence on toxic organic solvents.
18. Smith JD, Ansari TN, Andersson MP, Yadagiri D, Ibrahim F, Liang S, Hammond GB, Gallou F, Handa S: **Micelle-enabled clean and selective sulfonylation of polyfluoroarenes in water under mild conditions.** *Green Chem.* 2018, 20:1784–1790. <https://doi.org/10.1039/C7GC03514D>
19. Finck L, Brals J, Pavuluri B, Gallou F, Handa S: **Micelle-Enabled Photoassisted Selective Oxyhalogenation of Alkynes in Water under Mild Conditions.** *J. Org. Chem.* 2018, 83:7366–7372. <https://doi.org/10.1021/acs.joc.7b03143>
20. Vinci D, Donaldson M, Hallett JP, John EA, Pollet P, Thomas CA, Grilly JD, Jessop PG, Liotta CL, Eckert CA: **Piperylene sulfone: a labile and recyclable DMSO substitute.** *Chem. Commun.* 2007, 1427–1429. <https://doi.org/10.1039/B616806J>
21. Sherwood J, De bruyn M, Constantinou A, Moity L, McElroy CR, Farmer TJ, Duncan, Raverty W, Hunt AJ, Clark JH: **Dihydrolevoglucosenone (Cyrene) as a bio-based alternative for dipolar aprotic solvents.** *Chem. Commun.* 2014, 50:9650–9652. <https://doi.org/10.1039/C4CC04133J>
22. Bora PP, Bihani M, Plummer S, Gallou F, Handa S: **Shielding Effect of Micelle for Highly Effective and Selective Monofluorination of Indoles in Water.** *ChemSusChem* 2019, 12:3037–3042. <https://doi.org/10.1002/cssc.201900316>

This article highlights the role of PS-750-M and the shielding effect of micelles for fluorination chemistry. The highly valued mono-fluorination of indoles was reported owing to site-specific solubility of the substrate and fluorinating reagent, which does not proceed in water and organic media.
23. Bihani M, Bora PP, Nachtegaal M, Jasinski JB, Plummer S, Gallou F, Handa S: **Microballs Containing Ni(0)Pd(0) Nanoparticles for Highly Selective Micellar Catalysis in Water.** *ACS Catal.* 2019, 9:7520–7526. <https://doi.org/10.1021/acscatal.9b02316>

This article describes an excellent example of organometallic nanoparticle catalysis using Ni(0)Pd(0) nanoparticles stabilized by PS-750-M based micelles. The challenging selective carbamate cleavage was reported in presence of various sensitive functionalities.
24. Sharma S, Buchbinder NW, Braje WM, Handa S: **Fast Amide Couplings in Water: Extraction, Column Chromatography, and Crystallization Not Required.** *Org. Lett.* 2020, 22:5737–5740. <https://doi.org/10.1021/acs.orglett.0c01676>

In this study, the authors developed a completely organic solvent-free methodology for amide couplings with fast reaction rates. This highly sustainable and efficient method was also explored for the synthesis of bioactive molecules.
25. Sharma S, Kaur G, Handa S: **Insights into Fast Amide Couplings in Aqueous Nanomicelles.** *Org. Process Res. Dev.* 2021, 25:1960–1965. <https://doi.org/10.1021/acs.oprd.1c00203>
26. Duong UT, Gade AB, Plummer S, Gallou F, Handa S: **Reactivity of Carbenes in Aqueous Nanomicelles Containing Palladium Nanoparticles.** *ACS Catal.* 2019, 9:10963–10970. <https://doi.org/10.1021/acscatal.9b04175>
27. Bihani M, Ansari TN, Finck L, Bora PP, Jasinski JB, Pavuluri B, Leahy DK, Handa S: **Scalable α -Arylation of Nitriles in Aqueous Micelles using Ultrasmall Pd Nanoparticles: Surprising Formation of Carbanions in Water.** *ACS Catal.* 2020, 10:6816–6821. <https://doi.org/10.1021/acscatal.0c01196>

This is a breakthrough example in micellar systems, where authors have disclosed that reactive intermediates like carbanions and ketiminates are stabilized in the micellar core of PS-750-M which are otherwise quenched in water. α -arylation of nitriles in aqueous micelles was explored in this article.
28. Shen T, Zhou S, Ruan J, Chen X, Liu X, Ge X, Qian C: **Recent advances on micellar catalysis in water.** *Adv. Colloid Interface Sci.* 2021, 287:102299. <https://doi.org/10.1016/j.cis.2020.102299>
29. Lim YH, Ong Q, Duong HA, Nguyen TM, Johannes CW: **Direct Conversion of Indoles to 3,3-Difluoro-2-oxindoles via Electrophilic Fluorination.** *Org. Lett.* 2012, 14:5676–5679. <https://doi.org/10.1021/ol302666d>
30. Zhu Y, Rawal VH: **Palladium-Catalyzed C₃-Benzoylation of Indoles.** *J. Am. Chem. Soc.* 2012, 134:111–114. <https://doi.org/10.1021/ja2095393>
31. Panferova LI, Smirnov VO, Levin VV, Kokorekin VA, Struchkova VI, Dilman AD: **Synthesis of 3-Fluoroindoles via Photoredox Catalysis.** *J. Org. Chem.* 2017, 82:745–753. <https://doi.org/10.1021/acs.joc.6b02344>

32. Wu ZJ, Xu HC: **Synthesis of C₃-Fluorinated Oxindoles through Reagent-Free Cross-Dehydrogenative Coupling.** *Angew. Chem. Int. Ed.* 2017, **56**:4734–4738. <https://doi.org/10.1002/anie.201701329>
33. Albericio F, El-Faham A: **Choosing the Right Coupling Reagent for Peptides: A Twenty-Five-Year Journey.** *Org. Process Res. Dev.* 2018, **22**:760–772. <https://doi.org/10.1021/acs.oprd.8b00159>.
34. Lau JL, Dunn MK: **Therapeutic peptides: Historical perspectives, current development trends, and future directions.** *Bioorg. Med. Chem.* 2018, **26**:2700–2707. <https://doi.org/10.1016/j.bmc.2017.06.052>
35. Gabriel CM, Keener M, Gallou F, Lipshutz BH: **Amide and Peptide Bond Formation in Water at Room Temperature.** *Org. Lett.* 2015, **17**:3968–3971. <https://doi.org/10.1021/acs.orglett.5b01812>
36. * Ansari TN, Jasinski JB, Leahy DK, Handa S: **Metal-Micelle Cooperativity: Phosphine Ligand-Free Ultrasmall Palladium(II) Nanoparticles for Oxidative Mizoroki–Heck-type Couplings in Water at Room Temperature.** *JACS Au* 2021, **1**:308–315. <https://doi.org/10.1021/jacsau.0c00087>
37. ** Ansari TN, Sharma S, Hazra S, Jasinski JB, Wilson AJ, Hicks F, Leahy DK, Handa S: **Shielding Effect of Nanomicelles: Stable and Catalytically Active Oxidizable Pd(0) Nanoparticle Catalyst Compatible for Cross-Couplings of Water-Sensitive Acid Chlorides in Water.** *JACS Au* 2021, **1**:1506–1513. <https://doi.org/10.1021/jacsau.1c00236>

This article demonstrates the new concept of amphiphile-metal interaction for phosphine ligand-free catalysis in water.

This article describes the synthesis of ligand-free oxidizable Pd(0) nanoparticles, which are highly active for the coupling of water-sensitive acid chlorides under aqueous environment. Interestingly, amphiphile stabilizes the Pd(0) NPs. This approach enabled ligand-free cross-couplings in water.